DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

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TRANSMITTED VIA FACSIMILE

Cynthia Chianese
Assistant Director, Regulatory Affairs
Janssen Pharmaceutica
P.O. Box 200
Titusville, NJ 08560-0200

Re: NDA 20-210
Propulsid (cisapride) Tablets
MACMIS File ID #6704

Dear Ms. Chianese:

This letter is in reference to Janssen Pharmaceutica's (Janssen) submission, dated May 5, 1998, of promotional materials under cover of Form FDA 2253 for Propulsid (cisapride) Tablets. This submission consisted of three promotional brochures identified as JPIPR604, JPIPR605, and JPIPR626. Janssen is promoting Propulsid by disseminating labeling pieces that are false or misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act) and regulations promulgated thereunder. Specific objections follow:

Promotion of Unapproved Uses

In each of the three promotional brochures listed above, Janssen suggests that the use of cisapride is not only effective in the treatment of nocturnal heartburn due to gastroesophageal reflux disease (GERD), but is also effective in treating ' This implication is derived from the presentation of data '

However, the approved product labeling states that "[t]here were no consistent effects on daytime heartburn, symptoms of regurgitation, or histopathology of the esophagus." Furthermore, not only is Janssen promoting unapproved uses, Janssen makes efficacy claims that are inconsistent with the cisapride new drug application clinical trial results.

This presentation also suggests that the use of cisapride is effective in regardless of cause. The approved product labeling, however, states that "Propulsid is indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease." Thus, to suggest that cisapride is effective in instead of restricting its use to only those suffering nocturnal heartburn due to GERD constitutes promotion of an unapproved use.

Lack of Fair Balance

In all three of these promotional brochures, Janssen has confined the presentation of the fair balance information to the back page of each brochure. Janssen fails to include on each page or spread a prominent reference to the presence and location of this distinct location of the presentation of the risk information associated with the use of this product. The approved product labeling contains a boxed warning presenting the contraindications to use of Propulsid with a list of drugs that inhibit the cytochrome P450 3A4 enzyme system of the liver. The use of Propulsid with these drugs may result in drug-drug interactions that cause serious cardiac arrhythmias. Because of the potentially fatal risks associated with the use of this product due to cardiac arrhythmias, without a reference on each spread to the important limitations concerning the appropriate use of this product, these brochures are lacking in fair balance or otherwise misleading.

Representation of Greater Efficacy than Demonstrated in Clinical Trials

In all three of these promotional brochures, Janssen presents the percentage of GERD patients with either poor esophageal peristalsis, incompetent lower esophageal sphincter (LES), and delayed gastric emptying. This presentation is also accompanied by three statements, under the heading "Propulsid benefit" that imply that the use of cisapride "assists esophageal clearance," "increases LES tone," and "promotes gastric emptying." Janssen notes in small type under this graphic presentation that these "Propulsid benefit[s]" were derived from pharmacologic studies rather than clinical studies. The approved product labeling for cisapride notes that "these clinical trials did not show a significant effect on LESP [lower esophageal sphincter pressure]...." Statements that cisapride "assists esophageal clearance," "increases LES tone," and "promotes gastric emptying" imply that the use of Propulsid can effect the underlying disease. Therefore, without disclosing that the use of the drug has no consistent effect on the histopathology of the esophagus is false or misleading.

Requested Actions

Janssen should immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved.

In addition, any new or revised information relating to the boxed warning, contraindications, warnings, precautions, and adverse events associated with the use of Propulsid, known to Janssen, should be incorporated in any new or revised promotional materials. Finally, Janssen should propose a plan to assure that existing promotional materials are revised in accord with the revised risk information.

Janssen should submit a written response to DDMAC on or before June 19, 1998, describing the steps that it has taken to ensure that these activities and the use of these materials have been suspended.

Janssen should address any correspondence or additional questions to the undersigned at the Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17 B-17, 5600 Fishers Lane, Rockville, Maryland 20857. DDMAC reminds Janssen that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #6704, in addition to the NDA number.

Sincerely,

Stephen W. Sherman, JD, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications